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PhRMA

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Dockets Management Branch
Food and Drug Administration
(**H**FA-**3**05)
5630 Fishers Lane
Rm. **1061**
Rockville, MD **20852**

Re: Docket No. 02N–0115; Risk Management of Human Drugs; 67 Federal Register **18230**

Dear Sir/Madam:

The following comments supplement those presented by the Pharmaceutical Research and Manufacturers of America (PhRMA) at the public hearing on this topic that was held on May 22, 2002. PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members invested over $30 billion during 2001 for the discovery and development of new medicines.

The FDA Public Hearing referenced above explored potential solutions to a variety of safety-related issues. It is critical to note that risk management is a multi-factorial process and not amenable to simple solutions. Many of the potential solutions hold promise; however, we should not presume that a solution is appropriate until its effectiveness has been validated by scientific study. Just as we require proof of efficacy before a new medicine is approved, we should require that methods to assess and manage risks also be based on scientific evidence.

Risk Assessment

Although the benefits and risks of a drug are largely defined prior to approval, the detection of rare events and a full appreciation of benefit-risk profile in a broader patient population generally become apparent only after extensive clinical experience. Companies devote substantial resources (both monetary and personnel) to identify and respond to safety signals from marketed products.

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Proposed measures to improve the identification of risks both before and after market approval must be carefully evaluated as to not only their benefit, but also the possible adverse impact upon the American healthcare system. For example, proposals to increase the volume of post-marketing adverse event reports (mandatory reporting, expansion of MedWatch Program) without measures to improve the quality of individual reports may actually obscure the detection of potential safety "signals" by also

amplifying "noise." A second general requirement to greatly enlarge the size of clinical trials in order to detect certain less common adverse drug reactions might delay patient access to important medical advances, without necessarily improving our understanding of safety under "real world" conditions. For example, an increase in required clinical trial exposure from 10,000 patients to 30,000 patients may still not detect a very rare event occurring in fewer than 1 in 10,000 patients while potentially delaying benefits to patients for some years. The use of untested methods of risk identification or assessment may also paradoxically divert attention and resources from the development of validated methods. For example, an unvalidated drug safety program that requires a patient to complete a safety questionnaire when refilling a prescription, would consume vast resources, provide data of uncertain relevance, and might potentially divert limited resources from research to validate a more promising safety program. Therefore, before any proposal for improving risk assessment becomes a standard, its effectiveness should be scientifically evaluated.

Risk Management

Risk management will require a broad variety of tools whose benefit must be scientifically proven. We need to develop a discrete set of validated risk management tools, each tool tailored to address a specific set of risk management issues. An ad hoc approach to risk management (each program using unique tools) is likely to place an undue burden on healthcare resources. Furthermore, over-reliance on intensive risk management tools (restricted access programs, extensive testing requirements) may have unintended consequences including denial of therapeutic benefits to appropriate patients. For example, restriction of a drug's availability to a limited number of "certified" pharmacies might prevent a person, dependent upon public transportation, from obtaining the therapy at the neighbourhood pharmacy. Risk communication may prove to be an important component of risk management plans; however, a discussion of risk outside the context of benefit is likely to have limited usefulness in improving safety. For example, a caution regarding HMG-CoA-associated rhabdomyolysis without a discussion of the benefits of this class of medicines may have a net negative public health effect (a large number of people might die from preventable ischemic heart disease in order to avoid rhabdomyolysis in a very small number of people).

The Importance of Collaboration

The current healthcare system in the United States is diverse and complex. No one party has sufficient authority, experience, or a mandate to change the healthcare system. For example, the FDA has little control over physician behaviour or licensure. Significant improvements in the benefit-risk ratio of medical interventions will require collaboration among many stakeholders, including regulatory agencies (FDA, state licensing boards}, academic institutions (for example the Centers for Excellence in Research and Therapeutics), pharmacists, providers, professional societies, and patient groups.

In conclusion, we welcome the leadership of the FDA as we work to improve the benefit-risk relation of medicines. The development of useful risk assessment strategies

and risk management tools will require a careful and scientific evaluation of potent risk reduction strategies. Our diverse and complex healthcare system necessitates collaboration among the various stakeholders in order to make significant improvements in patient safety and the public health. PhRMA member companies continue to be committed to help ensure the optimal use of medicines.

Sincerely,

Alan Goldhammer